Αλληλεπιδράσεις Κυττάρων Με την Εξωκυττάρια Μήτρα

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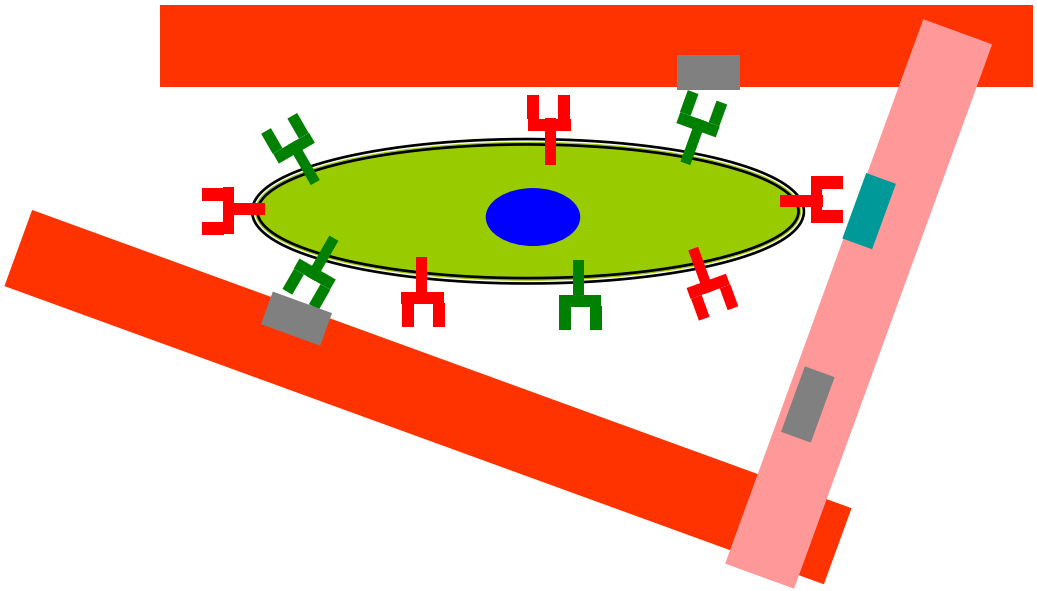
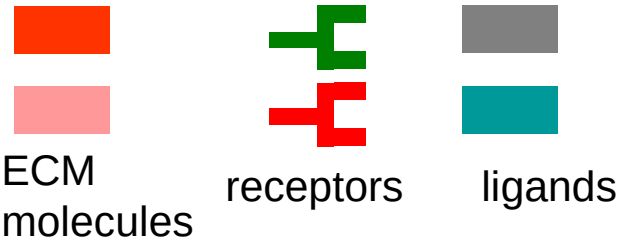
How Cells Interact with ECM

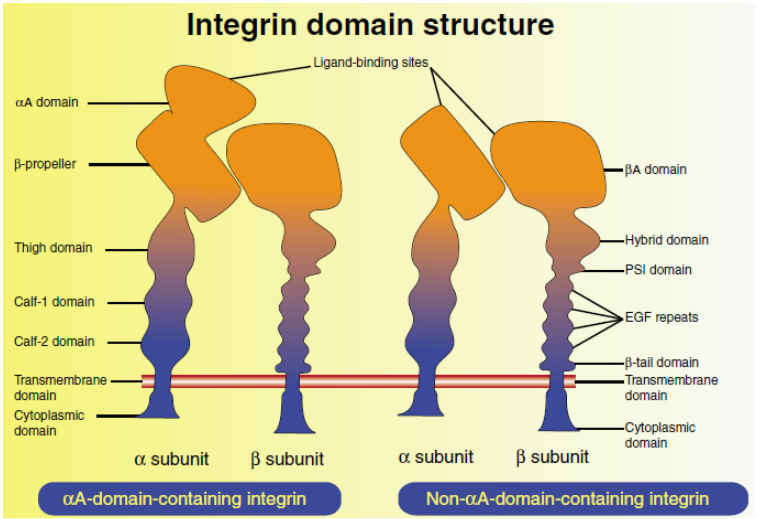
- Cells utilize adhesion receptors located on their cell membrane to bind motif (ligands) on ECM molecules



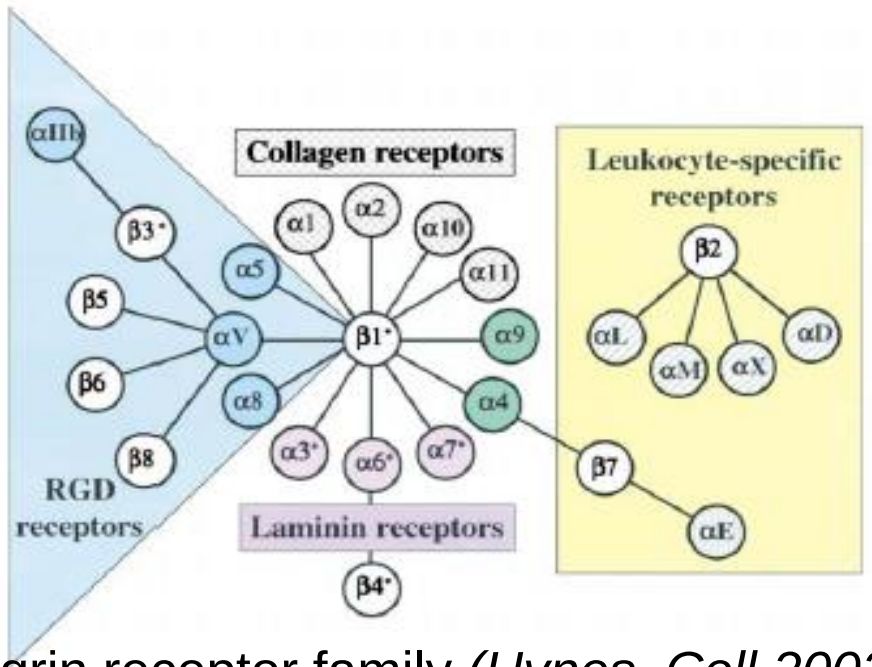


Adhesion Receptors

- Transmembrane proteins on cell membranes
- Grouped into families of structurally similar receptors that bind similar matrix molecules
- Integrins: the major family of adhesion receptors



Humphries et al., J. Cell Science 2006



Integrin receptor family *(Hynes, Cell 2002)*

Adhesion Receptors

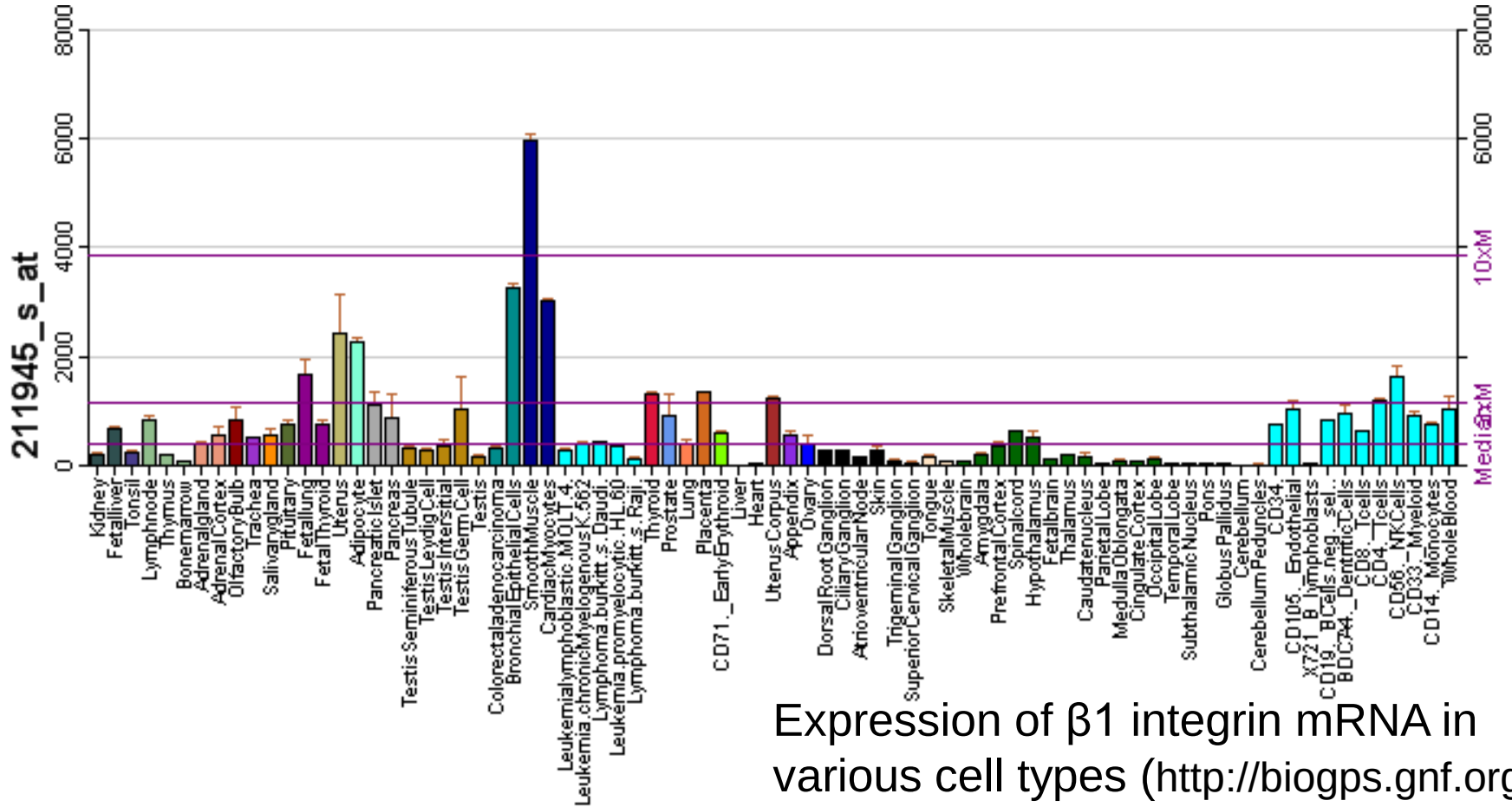
- Each adhesion receptor
  - can bind multiple biomolecules
  - sometimes binds the same molecule at multiple ligands
- Some matrix molecules bind to multiple AR

Ligand	Integrin
Adenovirus penton base protein	$\alpha_v\beta_3$, $\alpha_v\beta_5$
Bone sialoprotein	$\alpha_v\beta_3$, $\alpha_v\beta_5$
Borrelia burgdorferi	$\alpha_{IIb}\beta_3$
Candida albicans	$\alpha_M\beta_2$
Collagens	$\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_{11}\beta_1$, $\alpha_{IIb}\beta_3$
Denatured collagen	$\alpha_5\beta_1$, $\alpha_v\beta_3$, $\alpha_{IIb}\beta_3$
Cytotactin/tenascin-C	$\alpha_8\beta_1$, $\alpha_9\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_6$
Decorsin	$\alpha_{IIb}\beta_3$
Disintegrins	$\alpha_v\beta_3$, $\alpha_{IIb}\beta_3$
E cadherin	$\alpha_E\beta_7$
Echovirus 1	$\alpha_2\beta_1$
Epiligrin	$\alpha_3\beta_1$
Factor X	$\alpha_M\beta_2$
Fibronectin	$\alpha_3\beta_1$, $\alpha_3\beta_1$, $\alpha_4\beta_1$, $\alpha_4\beta_7$, $\alpha_5\beta_1$, $\alpha_8\beta_1$, $\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_{IIb}\beta_3$
Fibrinogen	$\alpha_5\beta_1$, $\alpha_M\beta_2$, $\alpha_v\beta_3$, $\alpha_x\beta_2$, $\alpha_{IIb}\beta_3$
HIV Tat protein	$\alpha_v\beta_3$, $\alpha_v\beta_5$
iC3b	$\alpha_M\beta_2$, $\alpha_x\beta_2$
ICAM-1	$\alpha_L\beta_2$, $\alpha_M\beta_2$
ICAM-2,3,4,5	$\alpha_L\beta_2$
Invasin	$\alpha_3\beta_1$, $\alpha_4\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$
Laminin	$\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_6\beta_1$, $\alpha_7\beta_1$, $\alpha_6\beta_4$, $\alpha_v\beta_3$
MAdCAM-1	$\alpha_4\beta_7$
Matrix metalloproteinase-2	$\alpha_v\beta_3$
Neutrophil inhibitory factor	$\alpha_M\beta_2$
Osteopontin	$\alpha_v\beta_3$
Plasminogen	$\alpha_{IIb}\beta_3$
Prothrombin	$\alpha_v\beta_3$, $\alpha_{IIb}\beta_3$
Sperm fertilin	$\alpha_6\beta_1$
Thrombospondin	$\alpha_3\beta_1$, $\alpha_v\beta_3$, $\alpha_{IIb}\beta_3$
VCAM-1	$\alpha_4\beta_1$, $\alpha_4\beta_7$
Vitronectin	$\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_{IIb}\beta_3$
von Willebrand factor	$\alpha_v\beta_3$, $\alpha_{IIb}\beta_3$

Binding partners of integrins in the ECM (Plow *et al.*, JBC, 2000)

Adhesion Receptors

- Cells express multiple adhesion receptors
- Each cell type expresses a different set of AR



Expression of β1 integrin mRNA in various cell types (http://biogps.gnf.org

Adhesion Ligands

- Locus on matrix molecule where adhesion receptor binds

- A molecule may contain multiple ligands
  - Collagen, Fibronectin

- Same ligand can exist in multiple biomolecules
  - e.g. RGD ligand

- Each ligand may bind to multiple adhesion receptors

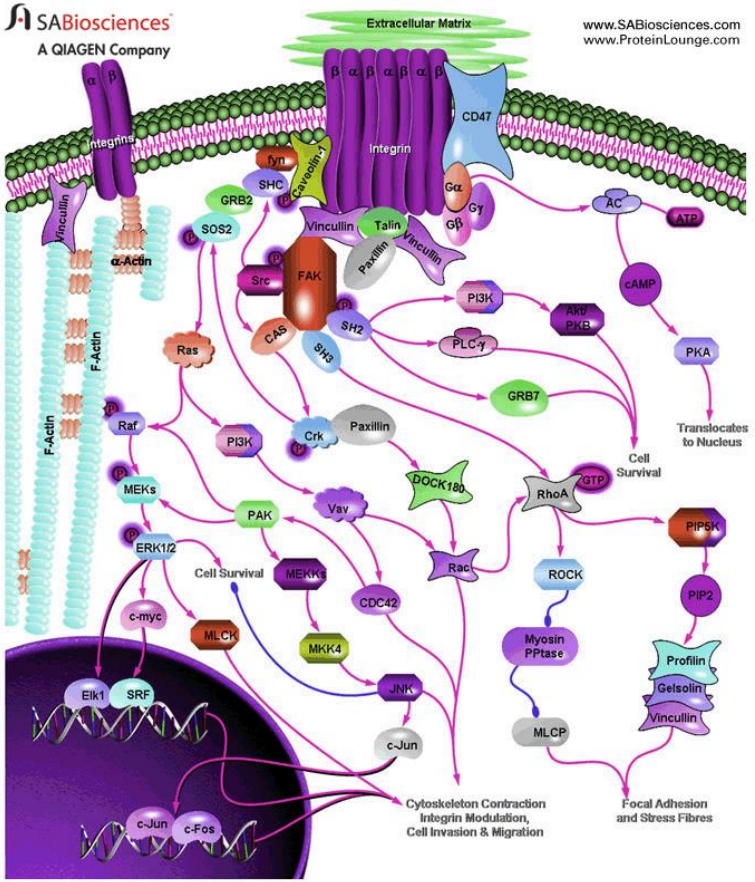
Recognition sequence	Ligand	Integrin
RGD	Adenovirus penton base protein, bone sialoprotein, collagen, decorsin, disintegrins, fibrinogen, fibronectin, prothrombin, tenascin, thrombospondin, vitronectin, von Willebrand factor	$\alpha_3\beta_1$, $\alpha_5\beta_1$, $\alpha_8\beta_1$, $\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_{IIb}\beta_3$
HHLGGAKQAGDV	γ-Chain of fibrinogen	$\alpha_{IIb}\beta_3$
GPR	α-Chain of fibrinogen	$\alpha_x\beta_2$
P1 peptide	γ-Chain of fibrinogen	$\alpha_M\beta_2$
P2 peptide	γ-Chain of fibrinogen	$\alpha_M\beta_2$
AEIDGIEL	Tenascin	$\alpha_9\beta_1$
QIDS	VCAM-1	$\alpha_4\beta_1$
LDT	MAdCAM-1	$\alpha_4\beta_7$
CS-1 peptide	Fibronectin	$\alpha_4\beta_1$, $\alpha_4\beta_7$
CS-5 peptide	Fibronectin	$\alpha_4\beta_1$
IDAPS	Fibronectin	$\alpha_4\beta_1$
ICAM peptides	ICAM-1, -2, -3	$\alpha_L\beta_2$, $\alpha_M\beta_2$
DLXXL	Tenascin	$\alpha_v\beta_6$
GFOGER[a]	Collagen	$\alpha_1\beta_1$, $\alpha_2\beta_1$

[a] O, hydroxyproline.

Integrin ligands (Plow *et al.* ,JBC, 2000)

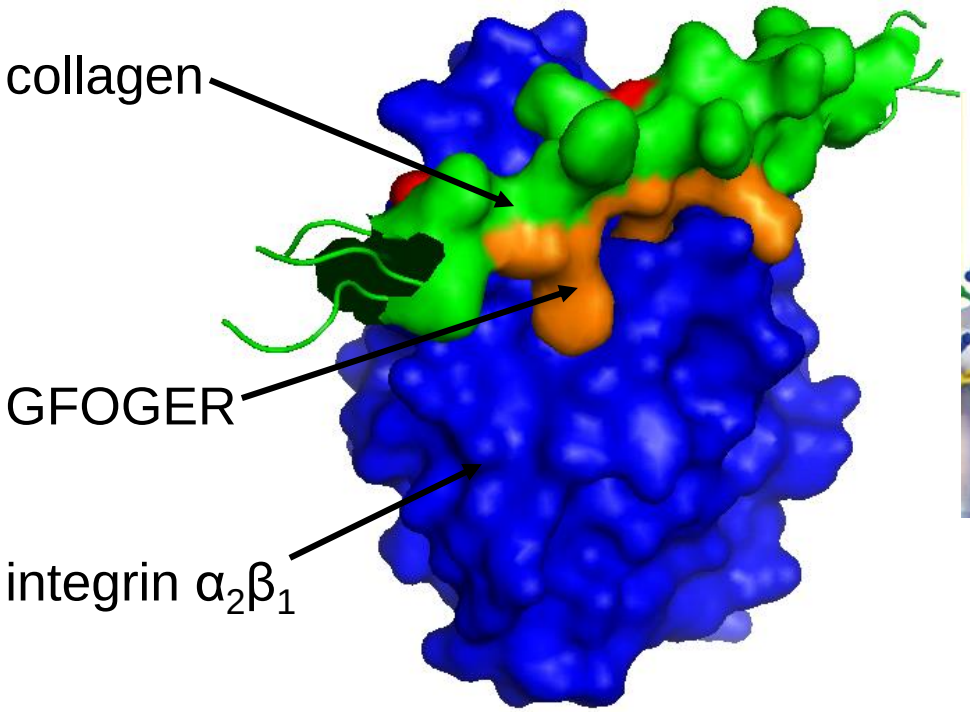
Adhesion-Induced Signal Transduction

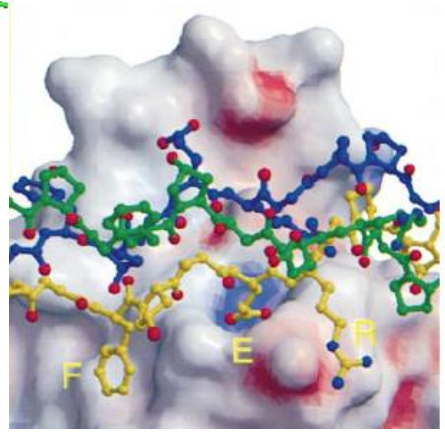
- Adhesion of AR to a ligand leads to intracellular signal transduction
  - Directly: AR signals directly by acting as a kinase
  - Indirectly: AR recruits kinases that signal
- Therefore, adhesion controls cell response and fate..

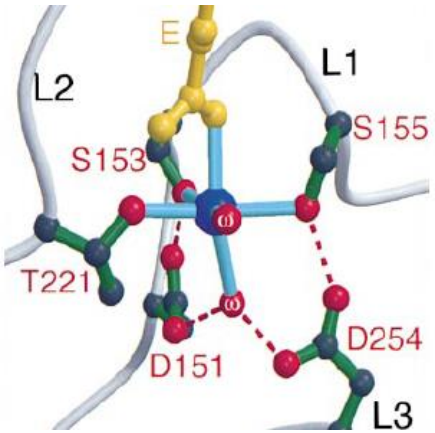


Case 1: Integrin-Collagen Adhesion

- The GFOGER motif is a ligand for integrins $\alpha_1\beta_1$, $\alpha_2\beta_1$
  - Cells do not bind collagen using the RGD ligand
- Binding is conformation dependent
  - $\alpha_1\beta_1$, $\alpha_2\beta_1$ bind collagen but not gelatin
- Binding requires Mg^{++}



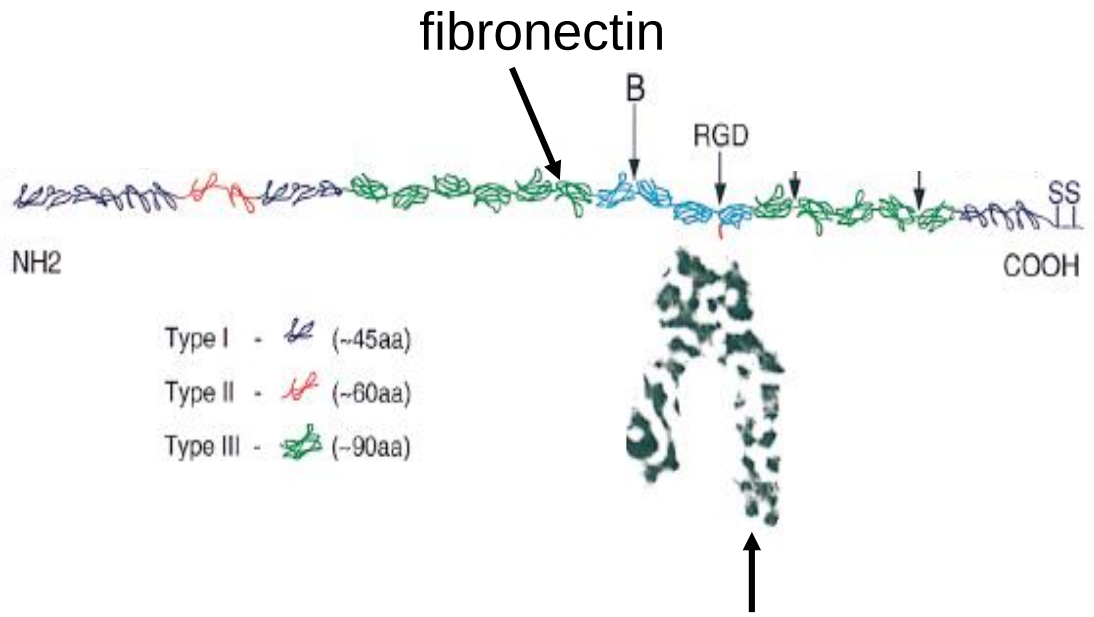




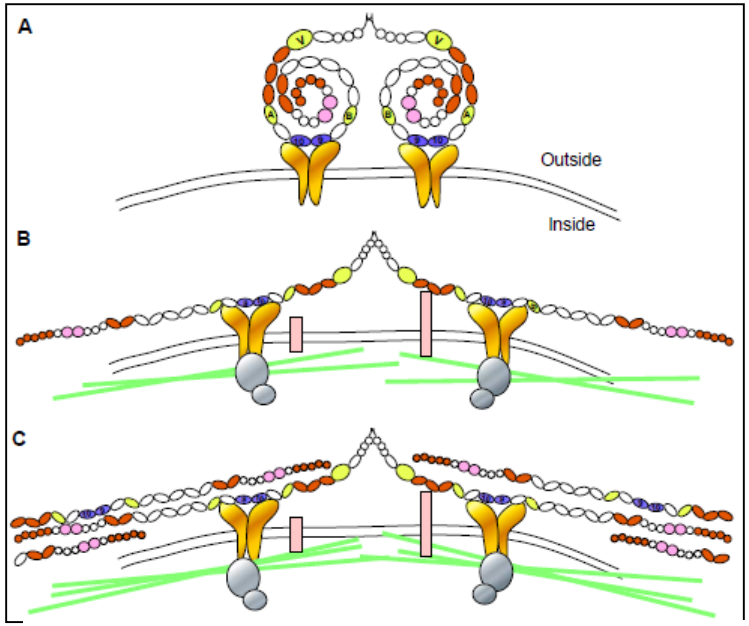
Emsley *et al.* , Cell, 2000

Case 2: Integrin-Fibronectin Adhesion

- RGD binding requires both integrin subunits
  - One subunit binds RGD, other binds “synergy site”
- Certain FN splice variants contain extra ligands
- Cell-secreted FN is globular.. Cell forces extend FN & expose ligands



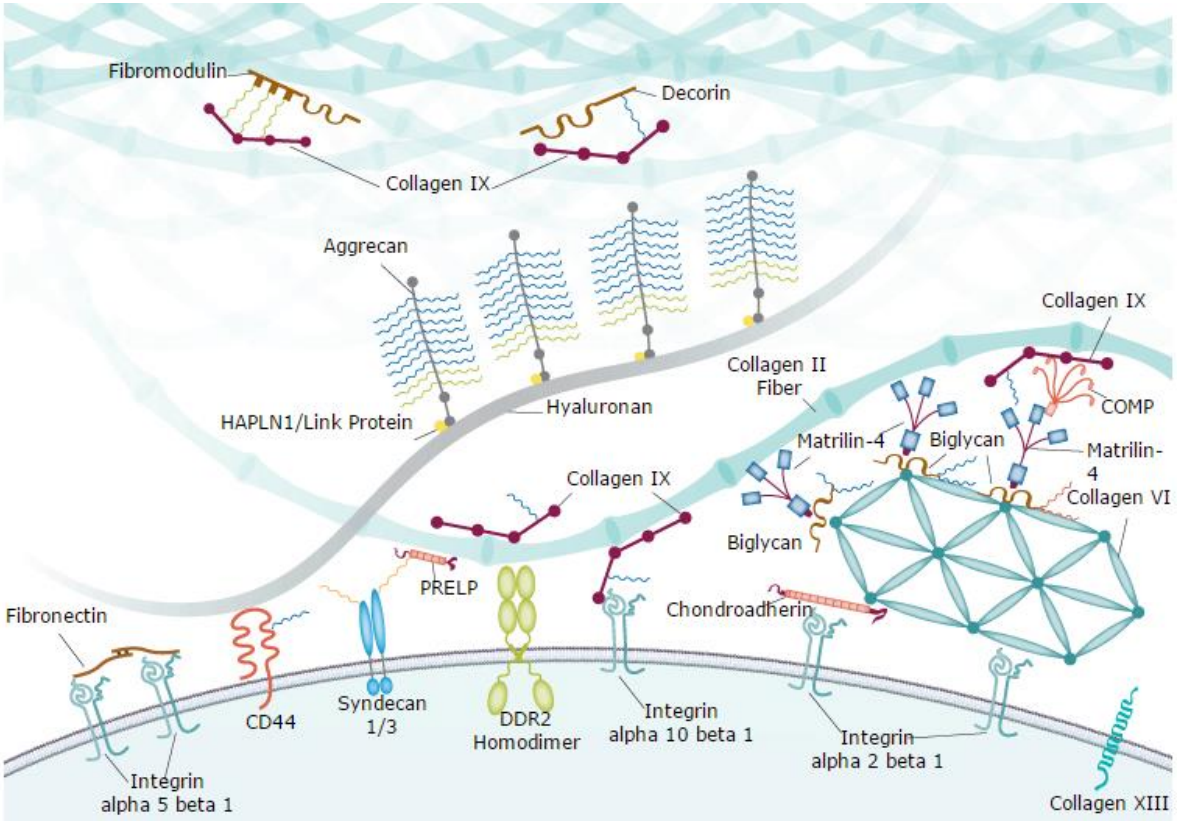
(Leahy et al. 1996)



Ligand exposure in FN (Mao & Schwarzbauer, 2005)

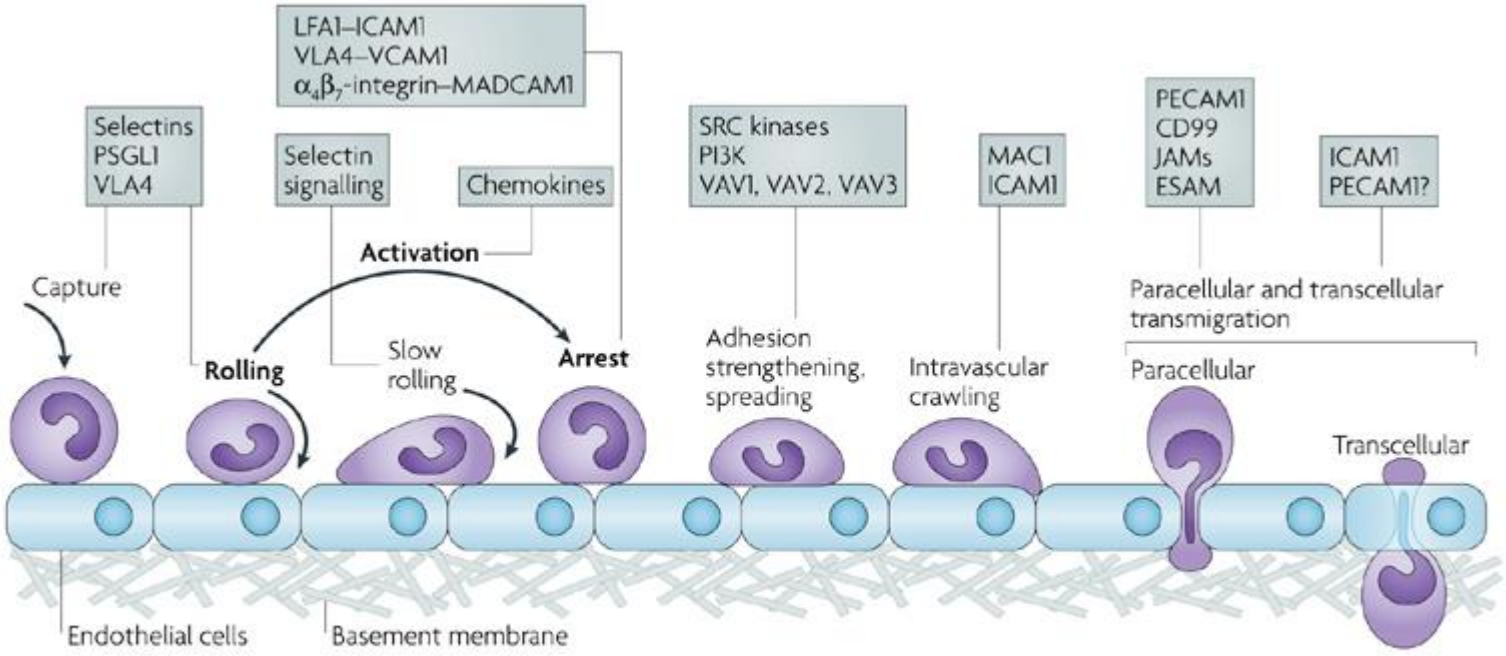
Case 3: Chondrocyte-ECM adhesion

- Chondrocytes utilize
  - Integrin α5β1 to bind fibronectin
  - Integrins α2β1, α10β1 and DDR2 to bind collagens
  - CD44 to bind hyaluronic acid



Case 4: Leukocyte rolling inside blood vessels

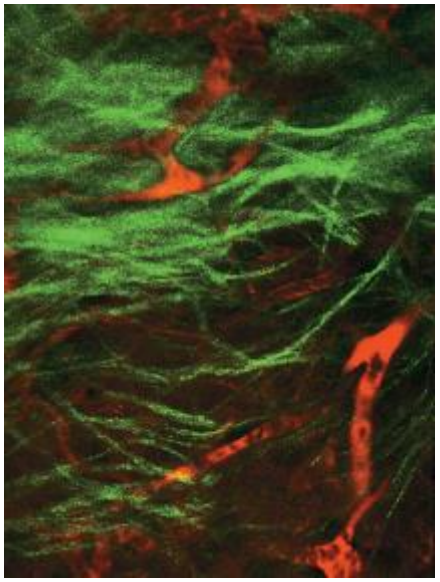
- Leukocytes use different set of AR to
  - Roll on the walls of the blood vessel (before activation)
  - Adhere to the well (before activation)
  - Interact with endothelia and transmigrate



Nature Reviews | Immunology

Case 5: Cell-matrix interactions in cancer

- Cancer cells produce denser & stiffer matrix than normal cells
  - Dense matrix → hypoxia → cells become more aggressive
  - Dense matrix → impedes drug delivery
  - Cancer cells apply larger forces → stiffens matrix → positive feedback



Tensional homeostasis and the malignant phenotype

Matthew J. Paszek,[1,2,6] Nastaran Zahir,[1,2,6] Kandice R. Johnson,[1,2] Johnathon N. Lakins,[2] Gabriela I. Rozenberg,[2] Amit Gefen,[3] Cynthia A. Reinhart-King,[1] Susan S. Margulies,[1] Micah Dembo,[4] David Boettiger,[5] Daniel A. Hammer,[1] and Valerie M. Weaver[2,*]

Tumors are stiffer than normal tissue, and tumors have altered integrins. Because integrins are mechanotransducers that regulate cell fate, we asked whether tissue stiffness could promote malignant behavior by modulating integrins. We found that tumors are rigid because they have a stiff stroma and elevated Rho-dependent cytoskeletal tension that drives focal adhesions, disrupts adherens junctions, perturbs tissue polarity, enhances growth, and hinders lumen formation. Matrix stiffness perturbs epithelial morphogenesis by clustering integrins to enhance ERK activation and increase ROCK-generated contractility and focal adhesions. Contractile, EGF-transformed epithelia with elevated ERK and Rho activity could be phenotypically reverted to tissues lacking focal adhesions if Rho-generated contractility or ERK activity was decreased. Thus, ERK and Rho constitute part of an integrated mechanoregulatory circuit linking matrix stiffness to cytoskeletal tension through integrins to regulate tissue phenotype.

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Multiphoton imaging of collagen (green) and blood vessels (red) in a tumor (Brown et. al. 2003)

Cell-Matrix Interactions Overview

- Cells perceive surrounding ECM via their adhesion receptors by binding ligands on ECM molecules
  - Adhesion via AR induces signaling that affects cells

- Different cells sense & respond to the same ECM in different ways
  - Each matrix molecule may contain multiple ligands
  - Each ligand may interact with multiple adhesion receptors
  - Different cell types express different sets of receptors

Summary

- Cells interact with the surrounding matrix (ECM, biomaterials) via their cell adhesion receptors (AR)
- Integrins: the major family of set adhesion receptors
- Each cell type express different set of AR
  - Different types of cells express different set of AR
  - Same matrix is perceived differently by different cell types
- Upon adhesion to their ligands on matrix molecules, AR induce downstream signal transduction that affects cells